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# **Some *distorted* thoughts about ketamine as a psychedelic and a novel hypothesis based on NMDA receptor-mediated synaptic plasticity**

Rachael Ingram<sup>1</sup>, Heather Kang<sup>2,3,4</sup>, Stafford Lightman<sup>2</sup>, David E. Jane<sup>3</sup>, Zuner A. Bortolotto<sup>3</sup>, Graham L Collingridge<sup>3,4</sup>, David Lodge<sup>3\*</sup> and Arturas Volianskis<sup>1,2\*</sup>✓

<sup>1</sup>Centre for Neuroscience and Trauma, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK

Centre for Synaptic Plasticity, <sup>2</sup>School of Clinical Sciences, <sup>3</sup>School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, UK

<sup>4</sup>Dept Physiology, University of Toronto and LTRI, Mount Sinai Hospital, Toronto, Canada

\*DL and AV are joint senior authors

## **✓Corresponding author:**

Dr. Arturas Volianskis

Centre for Neuroscience and Trauma

Blizard Institute, Barts and The London School of Medicine and Dentistry

4 Newark Street, London

E1 2AT

[A.Volianskis@qmul.ac.uk](mailto:A.Volianskis@qmul.ac.uk)

[A.Volianskis@bristol.ac.uk](mailto:A.Volianskis@bristol.ac.uk)

## **Keywords**

Psychedelics; Ketamine; Phencyclidine, PCP; NMDA receptors; GluN2D subunit; Short-term potentiation, STP; Long-term potentiation, LTP; Memory; Working Memory

## **Highlights**

1. Ketamine, an NMDA receptor (NMDAR) antagonist, is an atypical psychedelic.
2. Its psychedelic actions may involve multiple effects.
3. STP and LTP are distinct types of plasticity induced through activation of different NMDAR subtypes.
4. Ketamine blocks STP more potently than LTP, via an action on GluN2D-containing NMDARs.
5. Inhibition of STP is a novel candidate mechanism for some effects of ketamine.

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## Abstract

Ketamine, a channel blocking NMDA receptor antagonist, is used off-label for its psychedelic effects, which may arise from a combination of several inter-related actions. Firstly, reductions of the contribution of NMDA receptors to afferent information from external and internal sensory inputs may distort sensations and their processing in higher brain centres. Secondly, reductions of NMDA receptor-mediated excitation of GABAergic interneurons can result in glutamatergic overactivity. Thirdly, limbic cortical disinhibition may indirectly enhance dopaminergic and serotonergic activity. Fourthly, inhibition of NMDA receptor mediated synaptic plasticity, such as short-term potentiation (STP) and long-term potentiation (LTP), could lead to distorted memories. Here, for the first time, we compared quantitatively the effects of ketamine on STP and LTP. We report that ketamine inhibits STP in a double sigmoidal fashion with low (40 nM) and high (5.6  $\mu$ M)  $IC_{50}$  values. In contrast, ketamine inhibits LTP in a single sigmoidal manner ( $IC_{50}$  value  $\sim$  15  $\mu$ M). A GluN2D-subunit preferring NMDA receptor antagonist, UBP145, has a similar pharmacological profile. We propose that the psychedelic effects of ketamine may involve the inhibition of STP and, potentially, associated forms of working memory.

## Introduction

Shortly after the synthesis in the 1950s of phencyclidine (PCP) (Maddox et al., 1965) and later of ketamine (McCarthy et al., 1965), it became apparent that these two anaesthetics produced some bizarre central effects in both laboratory animals (Chen et al., 1959) and in man (Greifenstein et al., 1958; Meyer et al., 1959). The drugs produced a state of anaesthesia and analgesia with a good safety margin before lethality but poor muscle relaxation (see P. F. White et al., 1982). This unusual anaesthetic state was termed ‘dissociative’ after both the disrupted electroencephalographic patterns and the sensory deprivation with detachment from the real world (Domino et al., 1965; see Domino and Luby, 2012). The central effects, following either PCP or ketamine, include dizziness, nausea, delirium, confusion, disorientation, paranoia, amnesia, dysarthria, dysphoria with agitation, unpredictable aggression and delusions of extreme strength (Allen and Young, 1978; Domino et al., 1965; Luisada, 1978; Siegel, 1978a). Both drugs were known as psychotomimetics from the outset (Luby et al., 1959), and have been used to create animal models of schizophrenia (Cadindu et al., 2017; Frohlich and Van Horn, 2014; Javitt et al., 2012) but can they also be defined as psychedelics? Psychedelics are ‘*drugs (especially LSD [lysergic acid diethylamide]) that produce hallucinations and apparent expansion of consciousness*’ and hallucinations are experiences ‘*involving the apparent perception of something not present*’ (Oxford English Dictionary). There are hundreds of reports of hallucinations, visual, auditory and somatosensory, following exposure to ketamine and PCP.

For example, a recreational user of ketamine reported: ‘*... when I closed my eyes a lot of information started to happen. Colors, patterns, cross-connections in sensory perception. Like sound and inner visions sort of got confused. I got deeper and deeper into this state of realization, until at one point the world disappeared. I was no longer in my body. I didn't have a body. And I reached a point at which I knew I was going to die.... And what incredible feelings that evoked! . . . . I just*

*yielded. And then I entered a space in which . . .there aren't any words.....I mean, at-one-with-the-universe, recognizing-your-godhead.....The feeling was: I was home. That's really the feeling of it. And I didn't want to go anywhere, and I didn't need to go anywhere. It was a bliss state. Of a kind I had never experienced before. I hung out there awhile, and then I came back. I didn't want to come back. I guess in the deep state it was no longer than half an hour'.* Stafford, (1977), quoted in (Siegel, 1978b) who also quotes Young et al. (1977) likening *'this state to an LSD trip, only the ketamine tripper "feels as if he is floating in a dreamlike state while experiencing vivid visual images"'*. In fact, there are numerous reports noting similarities between experiences with LSD and ketamine. But ketamine, unlike classical psychedelics such as LSD, psilocybin, mescaline and dimethyltryptamine (DMT), is not a serotonin receptor agonist and its central effects in man can be distinguished from those of LSD, as described on psychonaut websites. In humans, serotonin-based hallucinogens and dissociative anaesthetics have psychedelic features in common, as well as abuse potential, and their mode of action may be linked by direct or indirect agonism of 5-HT<sub>2</sub> receptors (Heal et al., 2018; Sellers et al., 2017). In a standard psychometric test which scores five separate dimensions of altered states of consciousness (Dittrich, 1998), a classical psychedelic and ketamine showed similarities but clear differences (Vollenweider and Kometer, 2010). The profile following ketamine was skewed toward the dimensions of 'disembodiment' and 'experience of unity'. Furthermore, in behavioural studies in laboratory animals, the effects of LSD and PCP/ketamine are easily discriminated, suggesting a quite different mode of action (Carroll, 1990; Jones and Balster, 1998; West et al., 2000).

Drug discrimination studies in rats, monkeys, pigeons, etc, have, however found many drugs that do generalize to the PCP and ketamine cues. In the early 1980s, it became apparent that PCP and ketamine provided similar cues to other arylcyclohexylamines such as tiletamine, to benzomorphan sigma opiates such as SKF10,047 and cyclazocine, to dioxalanes such as dexoxadrol and etoxadrol, to morphinans such as dextrorphan and dextromethorphan, to benz(f)isoquinolines and to propanolamines such as 2-MDP (Brady and Balster, 1981; Brady et al., 1982a; 1982b; Herrling et al., 1981; Holtzman, 1982; 1980; Mendelsohn et al., 1984; Shannon, 1982a; 1982b; 1981; Tang et al., 1984; J. M. White and Holtzman, 1982). Such a list of compounds coincides with those also shown to displace PCP binding from rat brain tissue (Hampton et al., 1982; Murray and Leid, 1984; Quirion et al., 1981; Sircar and S. R. Zukin, 1983; Vincent et al., 1979; R. S. Zukin and S. R. Zukin, 1981; S. R. Zukin, 1982; S. R. Zukin et al., 1984; S. R. Zukin and R. S. Zukin, 1979).

Several of these compounds were already known to have similar bizarre subjective effects in man including hallucinations and were generally known as psychotomimetics (see Lodge and Mercier, 2015 for many of the chemical structures). Thus, beside arylcyclohexylamines PCP and ketamine (see above), the morphinans, dextromethorphan and dextrorphan, were originally described as producing 'toxic symptoms (dizziness, diplopia, etc)' (Isbell and Fraser, 1953). Benzomorphans including the 'sigma agonists', SKF 10.047 (Keats and Telford, 1964) and cyclazocine produce 'dose-related scores on the LSD scale' (Haertzen, 1970 quoted by Jasinski et al., 1967) and fuzzy thinking, illusions, dysphoria and frank visual hallucinations like LSD (Freedman and Fink, 1968; Jasinski et al.,



1967); such features were considered to be mediated by the sigma opiate receptor (Martin et al., 1976). The dioxalanes, dexoxadrol, (Lasagna and Pearson, 1965) and etoxadrol, induced 'dreams and/or visions that were pleasing .' (Frederickson et al., 1976).

Further contemporary support for this psychedelic effect of such compounds comes from a cursory examination of the web sites frequented by so-called psychonauts. This reveals that drugs such as ketamine, dextromethorphan, 2-MDP and compounds related to them are still frequently being used by humans. To avoid legal issues associated with ketamine use, new drugs for example, methoxetamine and arylethylamines, such as ephenidine, have come on to the market (Kang et al., 2016; Morris and Wallach, 2014; Wallach et al., 2016). During the last two weeks of January 2018, for example on one website, there were 35 reports of experiences with these and similar drugs (<https://erowid.org/experiences/exp.cgi?New>).

### **Sites of action of ketamine and PCP**

So do these compounds have a mechanism of action in common with classical psychedelics such as LSD, mescaline, psilocybin and dimethyltryptamine, which are all serotonergic ligands? It is generally believed that their agonist effect on 5-HT<sub>2</sub> receptors, particularly 5-HT<sub>2A</sub> receptors, is the basis for their psychedelic effects (Nichols, 2004; Vollenweider and Kometer, 2010). Activation of 5-HT<sub>2A</sub> receptors also increases glutamate release and firing of pyramidal neurones in the cerebral cortex by both pre-and post-synaptic mechanisms (Marek and Aghajanian, 1999; Vollenweider and Kometer, 2010), a finding in common with ketamine (discussed below). One group of authors have suggested that ketamine and PCP hallucinogenic activity may result from agonism of 5-HT<sub>2</sub> and dopamine (D<sub>2</sub>) receptors (Kapur and Seeman, 2002) but this appears not to be widely accepted and has not been proposed to explain the similar central effects of morphinans, benzomorphans, dioxalanes, etc. Conversely, activation of 5-HT<sub>2A</sub> receptors has been proposed to antagonise some of the neurotoxic effects of ketamine and PCP (Farber et al., 1998).

Nicotinic and muscarinic acetylcholine receptors have also been considered as part of ketamine's action with activity in the low micromolar range on  $\alpha 3\beta 4$ , and  $\alpha 7$  subtypes (Moaddel et al., 2013). Phencyclidine, dextromethorphan and dextrophan have potencies of 7.0, 8.9 and 29.6  $\mu$ M respectively on  $\alpha 3\beta 4$  nicotinic receptors (Hernandez et al., 2000). In addition, phencyclidine and dextromethorphan were significantly more potent than MK-801 and SKF10,047 as nicotinic antagonists (Yamamoto et al., 1992). Such data do not fit with the known potencies of these drugs in behavioural assays (see Lodge and Mercier, 2015). The stereoselectivity shown for example by dexoxadrol/levoxadrol and by the isomers of 3-methyl-PCP in behavioural assays (Browne and Welch, 1982; Marwaha et al., 1981) was not apparent in nicotine antagonism (Purifoy and Holz, 1984).

A similar argument pertains to sigma receptors. Several of the drugs producing ketamine-like psychedelic affects in man are also known as sigma agonists and their use as ligands for sigma receptors has confused the field. Nevertheless the prototypical agonists for both sigma<sub>1</sub> and sigma<sub>2</sub> receptors, namely haloperidol, (+)-3-PPP (*N-n*-propyl-3-(3-hydroxyphenyl)piperidine) and DTG (ditolylguanidine), do not have established psychedelic properties.

The common feature that does, however, link the above psychedelics is their ability to antagonise the actions of NMDA. Following the initial observations that ketamine and phencyclidine blocked both NMDA receptor-mediated polysynaptic reflexes (Lodge and Anis, 1984) and the direct agonist action of NMDA (Anis et al., 1983), the studies were extended to compounds that displace phencyclidine binding on CNS tissue and that generalize to phencyclidine cues in discrimination assays (for review and references see Lodge and Mercier, 2015). There were good correlations between potency of compounds as NMDA receptor antagonists and their potency in PCP binding assays and in drug discrimination assays (Lodge and Mercier, 2015). In particular, the stereoselectivity of compound pairs, such as dexoxadrol vs. levoxadrol, (+) vs (-)-3-methyl-PCP and (+) vs (-)-2-MDP, in both PCP binding and behavioural assays in laboratory rodents and primates was reproduced in tests of NMDA receptor antagonism (Lodge and Mercier, 2015). It seems therefore a very strong hypothesis that their psychedelic effects in man are explained by NMDA receptor antagonism. The above compounds do not act competitively as NMDA receptor antagonists (Lodge and Johnston, 1985; Martin and Lodge, 1985) but rather block the associated calcium-permeable channel function (MacDonald et al., 1987). In support of the above hypothesis, psychotomimetic effects have been reported in man following administration of competitive NMDA receptor antagonists (Davis et al., 2000; Grotta et al., 1995; Herrling, 1997; Muir, 2006).

### **Effects of ketamine on central information processing**

So the question arises as to why does NMDA receptor antagonism induce psychedelic effects? Here we discuss three potential mechanisms based on NMDAR antagonism that individually or collectively could contribute to these effects.-

1. Direct and / or indirect activation of dopaminergic pathways has been proposed to underlie the psychotomimetic effects of ketamine and related compounds.

2. A reduction in synaptic transmission through afferent pathways in which NMDA receptors play an important role will alter the sensory input to primary, secondary and association cerebral cortices and result in marked changes in perceived images.

3. NMDA receptors play a critical role in synaptic plasticity, such as long term potentiation (LTP), short term potentiation (STP) and long term depression (LTD). So the encoding and recall of recent or ongoing events/experiences will be affected by changes in NMDA receptor-dependent synaptic plasticity.

1. Dopaminergic modulation: Hyperdopaminergic activity, probably via D<sub>2</sub> receptor activation, has long been considered part of the psychedelic effect of phencyclidine and ketamine (Wise, 1996). Typical and atypical antipsychotics are effective against their psychotomimetic effects (Freeman and Bunney, 1984). Ketamine is a weak agonist at D<sub>2</sub> receptors (Frohlich and Van Horn, 2014) and increases release and inhibits uptake of dopamine, and other monoamines (Garey and Heath, 1976; Vickroy and Johnson, 1982); burst firing of

dopaminergic neurones essential for the release of dopamine, is dependent on NMDA receptor activation (Chergui et al., 1993; Zweifel et al., 2009). However, another major influence is likely to be disinhibitory changes in limbic control of dopaminergic neurones (Boley et al., 2014; Coyle et al., 2010; Jentsch and Roth, 1999; Moghaddam and Krystal, 2012; Nakazawa et al., 2012; Olney and Farber, 1995; Kokkinou et al., 2018; Lewis, 2014), as described below.

2. Altered sensory inputs: Disruption of signalling pathways, conveying information from sensory inputs to brain areas that are responsible for conscious perception, is an obvious candidate to explain psychedelic actions. Indeed, since the works of Edgar Adrian it has been known that sensory information is encoded in the frequency and number of action potentials (Adrian, 1928). Activity patterns of all central neurones are dependent on the balance between excitatory and inhibitory synaptic inputs, i.e. the complex temporal and spatial summation of the activity and efficacy of the afferents inputs to each neurone. The major transmitters mediating these excitatory and inhibitory inputs in higher centres of the brain are glutamate and GABA respectively, and these glutamatergic and GABAergic afferent neurones are themselves subject to the same excitatory and inhibitory influences. Glutamate receptors, and in particular NMDA receptors, due to their slow activation and deactivation kinetics, are uniquely placed to regulate patterns of neuronal firing. Excitatory synapses onto most, if not all, central neurones use both AMPA and NMDA receptors, the latter becoming more important with increasing frequency of the afferent action potentials and the depolarization of the subsynaptic membrane. Indeed, NMDA receptor antagonists are much more effective against synaptic events induced by high frequency discharges compared to low frequency ones (Herron et al., 1986; Salt, 1986). Therefore, changes in the relative contribution of subtypes of glutamate receptor throughout the neuraxis will influence the nature of the high frequency afferent signals into and between higher brain centres (Fig. 1) and thereby distort perceptual processes.

In the last few decades it has become established that NMDA receptors play an important role at excitatory synapses on parvalbumin (PV)-containing interneurons in the cerebral cortex (Cadinu et al., 2017; Goldberg et al., 2003; Grunze et al., 1996; Jones and Bühl, 1993; also see below). So ketamine is likely to reduce the influence of these neurones, which play an important role in fine-tuning responses of cortical pyramidal neurones (Agetsuma et al., 2017; Frohlich and Van Horn, 2014; Lee et al., 2017; Miao et al., 2017; Natan et al., 2017). Similarly ketamine-induced disinhibition via NMDA-sensitive PV-containing GABAergic neurones occurs in other brain areas including thalamus and hippocampus, disrupting their modulatory role on principal neurones (Steullet et al., 2017; Xia et al., 2017; Ye et al., 2018). Thus, changes in oscillatory function affecting cognitive ability (Uhlhaas and Singer, 2006) can result from selective inhibition of interneurone subtypes by ketamine (Middleton et al., 2008). Similar disinhibition by ketamine in the hippocampus, pallidum or pontine tegmentum could increase the number of bursting dopaminergic neurones of the ventral tegmentum (see Grace, 2010; Lodge et al., 2009)).

NMDA receptors are not a homogeneous entity (Hollmann and Heinemann, 1994; Monyer et al., 1992). They are composed of tetraheteromeric assemblies containing various combinations of GluN1, GluN2 and GluN3 subunits.

NMDA receptor expression is both regionally and developmentally regulated and it has been shown that the subunit composition of presynaptic, postsynaptic, perisynaptic and extrasynaptic NMDA receptors is not the same. GluN1 and GluN3 subunits bind the co-agonist glycine whereas GluN2 subunits bind glutamate itself. Relatively little is known about the functional roles of GluN3 subunits and no pharmacological tools exist that target them selectively. The functions of NMDA receptors composed of GluN1 and GluN2 subunits have been investigated in greater detail (Monyer et al., 1994; Vicini et al., 1998; Wyllie et al., 2013). Thus, diheteromeric NMDA receptors, which are composed of two GluN1 and two identical GluN2 subunits, are thought to be expressed in juvenile animals and in both synaptic and non-synaptic sites. In contrast, triheteromeric NMDA receptors contain two different GluN2 subunits in addition to the two GluN1s and are also widely expressed in the brain (Stroebel et al., 2018). Functional activation of NMDA receptors requires binding of both glutamate and glycine and, in addition to that, depolarization of the neuronal membrane is required to relieve the  $Mg^{2+}$  block from the NMDA receptor ion pore (Mayer et al., 1984; Nowak et al., 1984). It is here, close to the  $Mg^{2+}$  binding site of the tetramer, where dissociative anesthetics, such as PCP and ketamine bind (MacDonald et al., 1987; Song *et al.*, 2018). Importantly, it is the identity of the GluN2 subunits that confers distinct pharmacological and biophysical properties to the specific NMDA receptor assemblies, such as the affinity to bind glutamate, open channel kinetics, duration of the agonist evoked currents and the susceptibility of the receptors to the  $Mg^{2+}$  block (Hollmann and Heinemann, 1994; Monyer et al., 1994; Stroebel et al., 2018; Vicini et al., 1998; Wyllie et al., 2013).

The ability of the NMDA receptor-channel blockers such as PCP and ketamine to antagonize NMDA receptors depends on the state of the receptors since the binding site for the channel blockers is less available whilst under  $Mg^{2+}$  block. At negative membrane potentials,  $Mg^{2+}$  substantially, though not fully, blocks GluN2A/2B subunit-containing NMDA receptors and limits their contribution to synaptic transmission despite agonist availability. Pertinently, GluN2C/2D containing NMDA receptors are blocked less effectively by  $Mg^{2+}$ , and hence they contribute more appreciably to low frequency synaptic events (Schwartz et al., 2012). The competition with  $Mg^{2+}$  explains the lower  $IC_{50}$  values for the blockade of GluN2C/2D than for GluN2A/2B containing NMDA receptors by ketamine and other NMDAR channel blockers (Dravid et al., 2007; Kotermanski and Johnson, 2009; Kotermanski et al., 2009). GluN2C containing NMDA receptors are highly expressed in the cerebellum whereas GluN2Ds are prevalent throughout the brain, in both excitatory and inhibitory neurons. Thus, due to the higher affinity and due to the ability to block NMDA receptors at resting membrane potentials (Schwartz et al., 2012), both PCP and ketamine are likely to distort the processing of sensory information through inhibition of GluN2C/2D containing NMDA receptors. The finding that GluN2D subunits are relatively highly expressed in parvalbumin-expressing GABAergic interneurons helps explain the marked cortical disinhibition and hence changes in sensory inputs and processing that result from ketamine administration (Fig. 2). Interestingly, the ability of the dissociative anaesthetic, phencyclidine, to enhance striatal and prefrontal dopamine levels and to increase locomotor activity were absent in GluN2D knock-out mice (Hagino *et al.*, 2010; Yamamoto *et al.*, 2013) suggesting the possibility that this subunit could also be important

for the psychedelic effects of ketamine. Consistent with this, ketamine-induced increases in the power of cortical gamma oscillations involves the GluN2D subunit (Sapkota *et al.*, 2016).

### 3. Changes in synaptic plasticity:

In addition to their roles as mediators of fast synaptic transmission, NMDA receptors are essential for many plasticity processes throughout the CNS, in particular LTP and LTD (Collingridge *et al.*, 1983; Dudek and Bear, 1992; Volianskis *et al.*, 2015). These processes are believed to be important for learning and memory (Bliss and Collingridge, 1993; Martin *et al.*, 2000). Interestingly, unaware at the time that dissociative anaesthetics are NMDA receptor blockers, Guyenet's group found that both phencyclidine and ketamine (Stringer and Guyenet, 1983) and cyclazocine (Stringer *et al.*, 1983) prevent the induction of LTP. This effect of ketamine on LTP, first described in the hippocampal CA1 region, has been observed in other brain regions, including the prefrontal cortex (Rame *et al.*, 2017) visual cortex (Fathollahi and Salami, 2001) dentate gyrus (Zhang and Levy, 1992) and spinal cord (Benrath *et al.*, 2005).

Importantly, there is differential involvement of NMDA receptor subunits in the various aspects of synaptic plasticity. For example, it has been shown that induction of LTP in the CA1 region of adult rodents requires mainly activation of GluN2A/2B containing triheteromeric NMDA receptors (Volianskis *et al.*, 2013a). In contrast, STP, which is frequently co-induced with LTP (see Fig. 3), comprises two pharmacologically and kinetically distinct components (termed STP1 and STP2), the latter of which involves the activation of GluN2B and GluN2D containing NMDARs (Fig. 4, France *et al.*, 2017; Volianskis *et al.*, 2013a). It can be predicted that ketamine, due to its greater ability to block GluN2D containing NMDA receptors, may, therefore, preferentially inhibit the GluN2D sensitive STP2 over LTP. Consistent with this hypothesis, it has been demonstrated that MK-801 is more potent at blocking STP than LTP (Coan *et al.*, 1987). Although the effects of ketamine on LTP have been examined in detail (e.g. Ribeiro *et al.*, 2014), its ability to block STP has never been determined quantitatively. We have therefore assessed ketamine's inhibition of STP and LTP in dorsal hippocampal slices from adult rats in the presence of 2 mM Mg<sup>2+</sup> (Fig. 5).

Application of theta-burst stimulation (TBS) in control experiments induced bi-exponential STP that declined slowly to a stable level of LTP (Fig. 5A, Ctrl, pink). STP was highly sensitive to the GluN2D-preferring antagonist UBP145 (10  $\mu$ M). UBP145 abolished the majority of STP whilst largely sparing LTP (Fig. 5A, orange). STP can be defined both by its amplitude and its decay time constants. From these values we calculated the STP "area" for individual experiments (Fig. 5B). STP was inhibited >90% and LTP was inhibited <10% by UBP145.

Due to the very slow, use-dependent, block of NMDA receptors by ketamine (Kang *et al.*, 2016) the slices were pre-incubated in ketamine-containing ACSF (2 mM Mg<sup>2+</sup>) for 1.5 hours before the start of the experiments at concentrations indicated in Fig. 5. The same concentration was then perfused throughout the experiments. 10  $\mu$ M ketamine's effects on STP were remarkably similar to those of UBP145 abolishing majority of STP while preserving most of the LTP (blue curve Fig. 5A, and Fig. 5B). This was further examined by

determining full concentration response relationships for ketamine's effects on STP and LTP (Fig. 5C and D). Ketamine inhibited STP in a bi-sigmoidal fashion with low (40 nM) and high (5.6  $\mu$ M)  $IC_{50}$  values that differed 140-fold. Higher concentrations of ketamine were needed for inhibition of LTP, which was blocked in a single sigmoidal fashion, with an  $IC_{50}$  value of 14.8  $\mu$ M. Maximal inhibition of STP was achieved before inhibition of LTP, confirming that ketamine blocks STP more potently than LTP.

Ketamine was ~370 fold more potent at inhibiting STP2 than LTP. We have anticipated a smaller difference based on the selectivity of ketamine for GluN2D vs GluN2A and GluN2B subunits in recombinant systems, in the presence of physiological concentrations of  $Mg^{2+}$  (described above). However, the block of synaptically-activated NMDA receptors by ketamine is highly voltage-dependent (Davies et al., 1988). Given that the GluN2A/2B containing NMDA receptors are located postsynaptically whereas the GluN2D containing NMDA receptors are most probably located presynaptically (Volianskis et al., 2013a), these receptor populations could readily experience differing degrees of depolarization.

Individual excitatory synapses have been shown to express STP, LTP or both (Debanne et al., 1999) and STP is observed in many cortical regions, including the visual cortex (Harsanyi and Friedlander, 1997a; 1997b) and the hippocampus (Malenka, 1991; Schulz and Fitzgibbons, 1997; Volianskis and Jensen, 2003). It has been shown that STP and LTP modulate synaptic transmission differently (Volianskis *et al.*, 2013b). Because STP involves an increase in the probability of neurotransmitter release ( $P(r)$ ) it alters the firing pattern within a high frequency burst discharge. In contrast, LTP does not affect  $P(r)$  and increases the responses within a high frequency burst discharge proportionately (Pananceau et al., 1998; Selig et al., 1999; Volianskis et al., 2013b).

The functions of STP in the CNS have not been extensively studied. However, STP has been observed during exploratory learning in rats (Moser et al., 1993; 1994). In contrast to LTP, which is thought to be involved in long-term storage of information in the brain, STP may be the physiological correlate of short-term / working memory (Volianskis *et al.*, 2013b; Volianskis et al., 2015). STP has a unique property that could be exploited for certain forms of working memory (Fig. 3B). Notably, once induced at a synapse STP does not decay passively but can be stored during periods of synaptic inactivity (Volianskis et al., 2013b; 2013a; Volianskis and Jensen, 2003). When the synapse is re-activated, and dependent on the frequency of the incoming inputs, STP will be either re-induced and maintained (during high-frequency activity) or depleted (during low frequency activation), leading to a decrease in synaptic efficacy back to initial values (Volianskis and Jensen, 2003). Interestingly, storage of information in inactive and silent neuronal networks has been recently suggested to mediate working memory in humans (Rose et al., 2016). STP may mediate the form of working memory that we use to remember an event in time and space, such as where we have placed our keys, or cell phone, or parked our car (Fig. 6). That is, a memory that we need to retain until accessed and then quickly forgotten, so that we can remember a different location for a similar activity.

The dissociation between the working and the long-term memories has been debated since the infamous discussion at the end of 19<sup>th</sup> century between

William James and Charles Richet (see James 1890 and Richet 1886). It was Richet who suggested that working memory processes are vital for perception of reality and also self-perception. "*Without memory no conscious sensation, without memory no consciousness*", he said. Ketamine's disruption of working memory, a classical feature of schizophrenia, is well documented in both animals and humans (Adler et al., 1998; Kotermanski et al., 2013; Moghaddam and Krystal, 2012; Morgan and Curran, 2006) and on this basis, together with ketamine's high potency against STP, we hypothesize here that the psychedelic effects of ketamine are mediated in part by inhibition of STP and hence some aspects of working memory.

#### Conclusions:

Ketamine is a relatively selective NMDA receptor antagonist. Because NMDA receptors are known to contribute to synaptic events throughout the brain and spinal cord, ketamine will distort afferent information, processing in the cerebral cortex and output pathways. Specifically, because of their biophysical properties, NMDA heteromers containing the GluN2D subtype are particularly sensitive to ketamine. This relatively high potency of ketamine at GluN2D subunits and their importance in parvalbumin-containing GABAergic neurones and in STP at excitatory synapses provide a potential basis for the psychedelic actions of ketamine.

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## Figure legends; Ketamine as a psychedelic, Ingram et al 2018

### Figure 1. The balance between NMDA and AMPA receptors.

Information is transmitted from sensory receptors throughout the neuraxis by many excitatory synapses in afferent pathways. Each such glutamatergic synapse has both AMPA and NMDA receptors, the balance between relative contributions of each will depend on numerous factors. Such factors include the relative expression of each subtype, the nature of the subunits of these tetrameric receptors, temporal and spatial summation and postsynaptic membrane potential. Ketamine tips the balance and distorts the sensory information reaching higher centres by reducing the NMDA receptor contribution.

### Figure 2. Disinhibition distorts cortical processing of sensory information.

Output of principal neurones in sensory, motor and limbic cortices depends on afferent information that is subject to modulation by monoaminergic, fibres and by inhibitory influences, from amongst others feedforward and recurrent GABAergic interneurons. NMDA receptors play an important role in excitation of some of these inhibitory interneurons, in part because they are composed of the relatively  $Mg^{2+}$ -insensitive GluN2D subunits. Ketamine preferentially affects such receptors and results in disinhibition or overactivity of some principal neurones and as such distorts the information processing and the output of cerebral cortices. In the sensory cortex, this results in altered perception and the psychedelic state. In limbic cortices, this disinhibition can result in further increases in monoaminergic activity, potentially mimicking the effects of classical psychedelic drugs, lysergic acid diethylamide (LSD) and 2,5-dimethoxy-4-iodoamphetamine (DOI).

**Figure 3. STP and LTP in the CA1 area of the Schaffer-collaterals in the hippocampus** (according to (Volianskis et al., 2013b; 2013a; Volianskis and Jensen, 2003). High frequency stimulation (10 x theta-burst stimulation; TBS) induces NMDA receptor dependent short term potentiation (STP) and long term potentiation (LTP), both of which can be blocked by NMDAR antagonists. **(A)** STP declines to a stable level of LTP in a bi-exponential manner (STP1 & STP2) with time constants such as those shown in the inset. **(B)** STP does not decline passively if low frequency testing of synaptic strength is discontinued after delivery of TBS and only starts declining after resumption of the stimulation (Volianskis et al., 2013b; 2013a; Volianskis and Jensen, 2003). **(C)** TBS in the presence of GluN2A antagonists induces mostly STP2, which declines slowly. **(D)** TBS in the presence of GluN2D antagonists induces only STP1 and LTP. Synaptic potentiation can be completely blocked by combination of GluN2A and GluN2D antagonists (not shown).

**Figure 4. NMDA receptor pharmacology of STP and LTP.** STP and LTP are differentially inhibited by four, structurally different NMDA receptor antagonists (modified from (Volianskis et al., 2013a). STP and LTP are blocked in a double- and single-sigmoidal manner respectively. STP1, STP2 and LTP components and their corresponding  $IC_{50}$  values are given in the insets. (A) Prototypical NMDA receptor antagonist D-AP5 (B) GluN2A-preferring antagonist NVP-AAM077. (C)

Highly selective allosteric inhibitor of GluN2B subunits, Ro 25-6981. (D) GluN2D-prefering antagonist UBP145.

**Figure 5. Ketamine, like UBP145, is more potent at blocking STP than LTP.** STP was induced by 30 x TBS (details below) and declined in a bi-exponential manner with fast (3.3 min) and slow (35.6 min) time constants to a stable level of LTP. Averaged data sets were fitted using Prism 7 (GraphPad), assuming shared decay time constants. Estimated parameters for STP and LTP are shown in the insets. **(A)** 10  $\mu$ M UBP145 (orange data) and 10  $\mu$ M ketamine (blue data) preferentially inhibit STP. The solid bar indicates application time for UBP145. Ketamine was pre-incubated for ~1.5 hours and throughout the remainder of the experiment (dashed bar). Insets show representative f-EPSPs for the three data sets at the time points that are indicated by the coloured letters (black = baseline, red = peak STP; green = LTP). **(B)** UBP145 and ketamine inhibit STP more effectively than LTP. \*\*  $P < 0.01$ . **(C)** Concentration dependency of the ketamine block of STP and LTP. **(D)** Ketamine is more potent at blocking STP than LTP. **METHODS:** Experiments were performed and analysed as described previously in detail (Volianskis et al., 2013b; 2013a; Volianskis and Jensen, 2003), using Schedule 1 methods and according to the UK Scientific Procedures Act, 1986 and EU guidelines for animal care. Briefly, transverse hippocampal slices from adult male Wistar rats (~10 weeks old, 200-220g, Charles River) were pre-incubated for ~1.5 h prior to addition of ketamine (Ketalar<sup>®</sup>) to the perfusate. Slices were then maintained in ketamine for ~1.5 h prior to TBS and thereafter for the remainder of the experiment. UBP145 was applied for 30 min prior to TBS. Slices were kept submerged at (~32 °C) and superfused at a rate of 2.5 ml/min with aCSF (in mM: 124 NaCl, 3.5 KCl, 1.25 NaH<sub>2</sub>PO<sub>4</sub>, 26 NaHCO<sub>3</sub>, 2 CaCl<sub>2</sub>, 2 MgSO<sub>4</sub> and 10 glucose), which was saturated with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. Field excitatory postsynaptic potentials (f-EPSPs) were recorded in the CA1-B area of stratum radiatum. After a stable period of at least 30 min (baseline) theta-burst stimulation (TBS, a burst of 4 pulses at 100 Hz repeated 30 times with an inter-burst interval of 200 ms) was given. Data were recorded using WinLTP software ((Anderson and Collingridge, 2007); [www.winltp.com](http://www.winltp.com)).

**Figure 6. The K-Hole.** Ketamine blocks STP and may, in this way, interfere with processes of working memory leading to distorted thoughts (background artwork by thejowking, <https://thejowking.deviantart.com>).

Fig 1. Ingram et al 2018

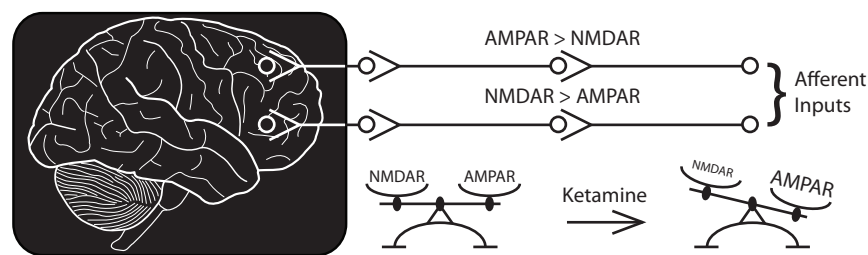


Fig 2. Ingram et al 2018

LSD, DOI and other psychedelics mimic such serotonergic inputs by presynaptic facilitation of glutamatergic inputs in sensory neurons

**Ketamine selectively affects synapses with larger NMDAR contribution; e.g., feed forward and recurrent inhibition**

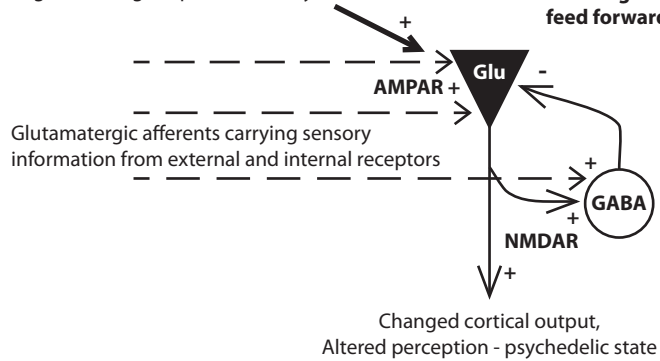


Fig 3. Ingram et al 2018

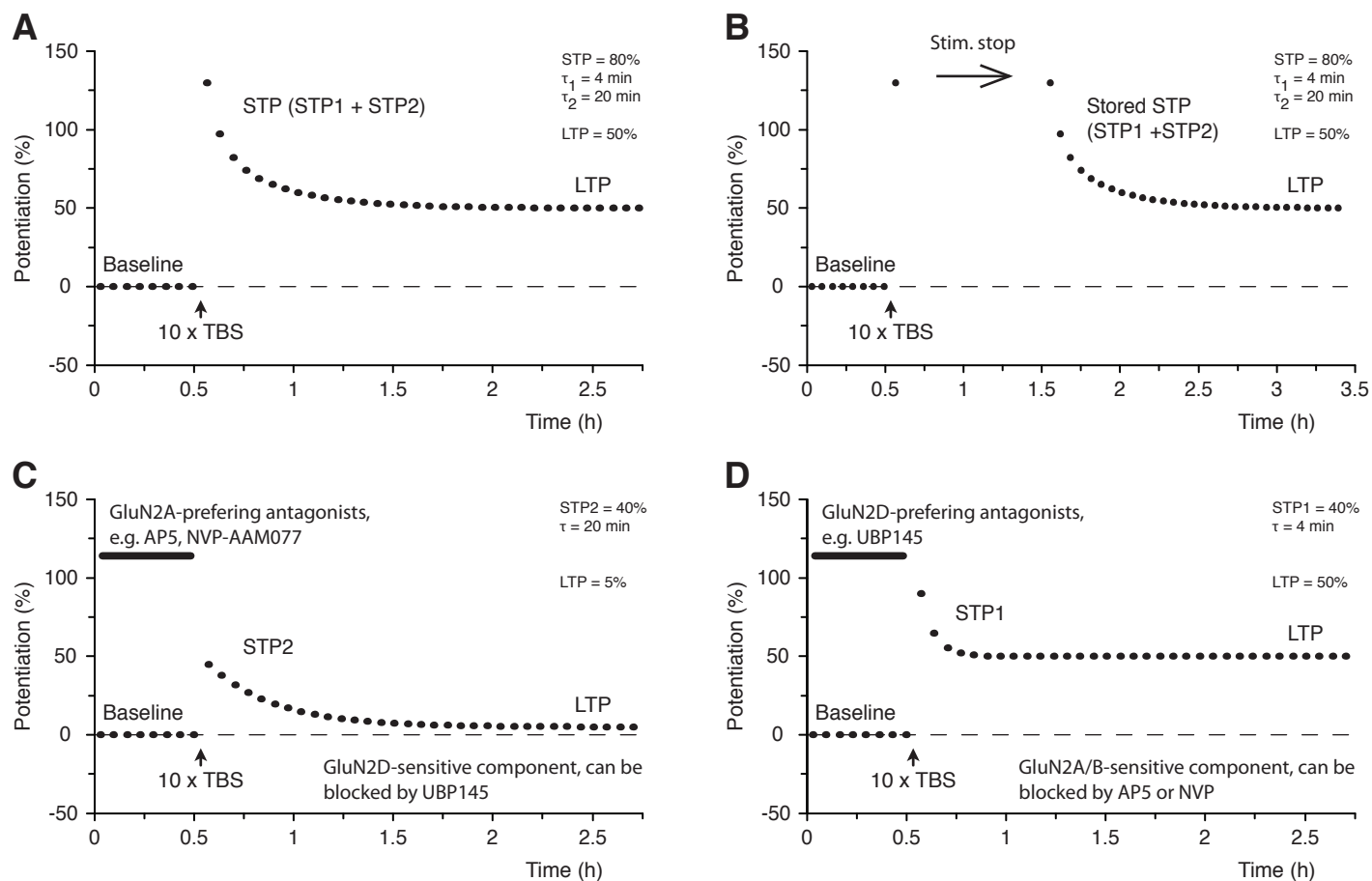


Fig 4. Ingram et al 2018

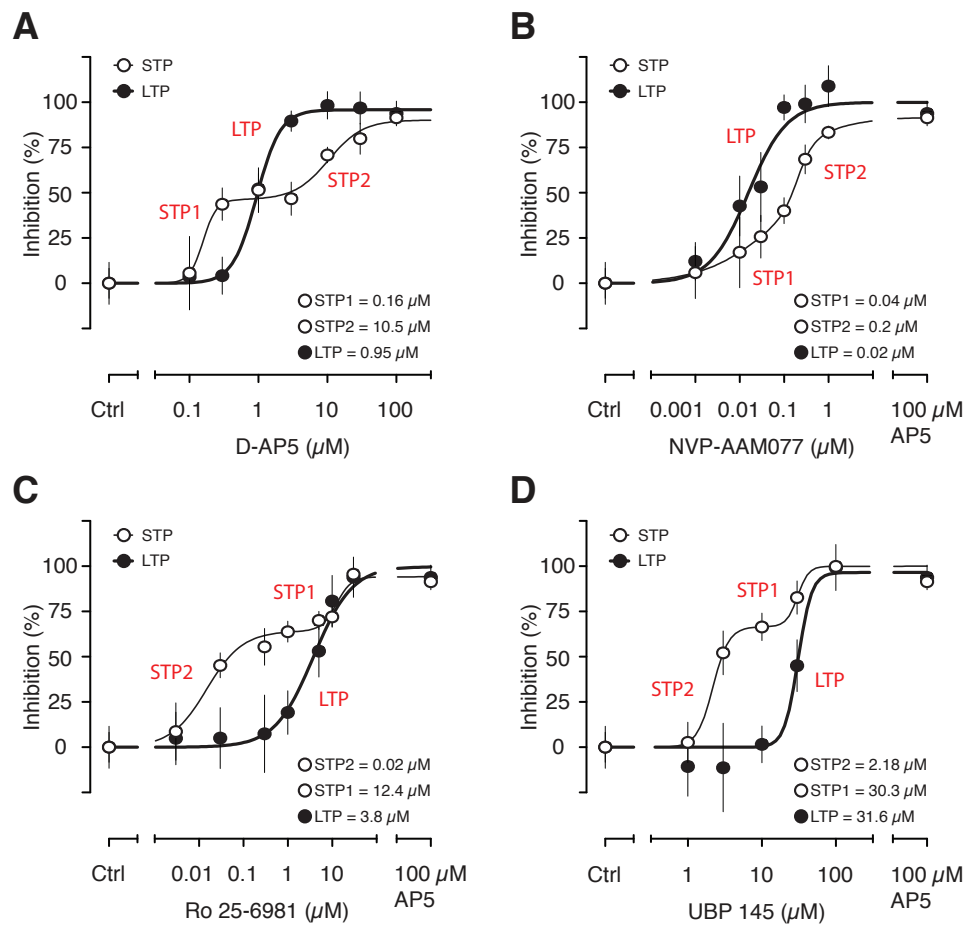


Fig 5. Ingram et al 2018

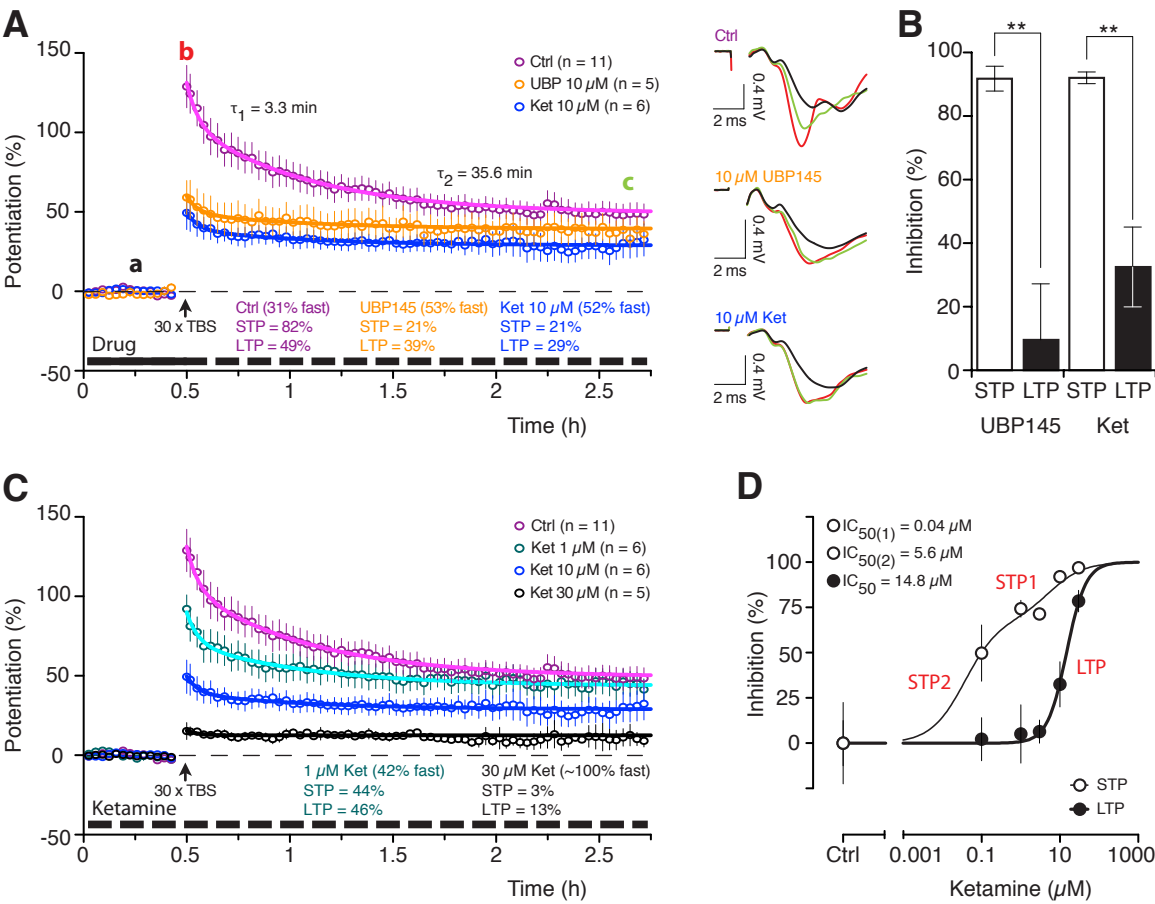




Fig 6. Ingram et al 2018

